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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/079,834 05/15/98 MOUNTZ

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EXAMINER

HM22/0323

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ART UNIT	PAPER NUMBER
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1644
DATE MAILED:

03/23/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/079,834

Applicant(s)
Mountz And Zhou

Examiner
Mary B. Tung

Group Art Unit
1644



☒ Responsive to communication(s) filed on Dec 27, 2000

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1, 3-6, and 8-16 is/are pending in the application

Of the above, claim(s) 10-15 is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☐ Claim(s) _____ is/are rejected.

☒ Claim(s) 1, 3-6, 8, 9, and 16 is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-17 were originally presented.
Claims 10-15 stand withdrawn from consideration.
Claims 2 and 7 were cancelled in the paper filed 2/1/99, Paper No. 5
Claim 17 was cancelled in the paper filed 12/3/99, Paper No. 11.
Claims 18 and 19 were cancelled in Paper No. 11.
Claims 18 and 19 were cancelled in Paper No. 19.
Claims 1, 3-6, 8, 9 and 16 are under consideration.

Claim Rejections - 35 U.S.C. § 103

1. In light of the amendment to claims 1 and 3-6 in Paper No. 19, the rejection under 35 U.S.C. 103(a) as being unpatentable over Bellgrau (US Patent No. 5,759,536) in view of Süss (*J. Exp. Med.* 183:1789-1796, 1996) is hereby withdrawn.
2. In light of the amendment to claims 1 and 3-6 under 35 U.S.C. 103(a) as being unpatentable over Bellgrau (US Patent No. 5,759,536) in view of Schuler, et al. (*Int. Arch. Allergy Immunol.* 112:317-322, 1997) is hereby withdrawn.
3. In light of the amendment to claims 16 under 35 U.S.C. 103(a) as being unpatentable over Bellgrau (US Patent No. 5,759,536) in view of Süss, et al. (*J. Exp. Med.* 183:1789-1796, 1996) is hereby withdrawn.
4. In light of the amendment to claim 16 under 35 U.S.C. 103(a) as being unpatentable over Bellgrau (US Patent No. 5,759,536) in view of Schuler, et al. (*Int. Arch. Allergy Immunol.* 112:317-322, 1997). is hereby withdrawn.

Claim Rejections - 35 U.S.C. § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
6. The rejection of claims 1, 3-6, 8, 9 and 16 under 35 U.S.C. 112, first paragraph, is hereby withdrawn.
7. The rejection of claim 19 under 35 U.S.C. 112, first paragraph, is hereby withdrawn.

The following new grounds for rejection are necessitated by amendment:

Claim Rejections - 35 U.S.C. § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 3-6, 8, 9 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of adenoviral vectors AdLoxFasL and AxCANCre in mice, does not reasonably provide enablement for said vectors in general, particularly in humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the current state of the art, scope of the claim, unpredictability in the art, the amount of experimentation required, and the amount of direction or guidance presented.

10. These claims would encompass the use of said vector in humans. The Applicants have not disclosed how one of skill in the art would be able to use an adenoviral vector in species other than mice. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. Besides the method inducing systemic immune tolerance in mice using an adenoviral vector (see pages 10-11 and Example 3, in particular), the specification fails to provide guidance as to a method of inducing systemic immune tolerance in a human, using an adenoviral vector. Anderson (*Nature* 392(suppl):25-30, April 1998) teaches that “[adenoviral trials] results in animals have not always reflected what happens in [human] patients” (bracketed term added by Examiner for clarity). Additionally, in response to the University of Pennsylvania adenoviral clinical study, wherein a study subject died, Fox (*Nature Biotechnology* 18:143-144, Feb. 2000), teaches that the safety characteristics of the adenoviral vector used by the U. Penn researchers (headed by James Wilson) were good, based on studies in mice. Fox also teaches that Wilson indicated that “the doses at which there are toxic effects or potential therapeutic effects may be separated only narrowly, and there may be thresholds where adverse effects abruptly appear - complicating how vectors might be used and perhaps undermining the reliability of results from tests in animals.” Also, “Equally, if not more problematic for would-be gene-therapy procedures, these vectors are not so reliable in delivering genes where they are targeted.” The adenovirus in the trial subject had “spread widely through other organs and also, at least early on, into immune system cells, based on the post mortem analysis of his tissues - distributing

quite differently from how it behaved during animal experiments, according to Wilson.” (see page 144). Furthermore, Marshall (*Science* 288:951-957, May 2000) teaches that “Relying on mouse studies, they [the Wilson team] had expected to see adenovirus concentrated in the liver. Instead, as a post mortem revealed, the vector was everywhere. To figure out what happened, Wilson gave the vector intravenously to mice. Tagged adenovirus vector first appeared in macrophage or scavenger cells in the liver.... Later it reached the intended target, primary liver cells (hepatocytes).” “Animal data may have given clinicians false hope that adenovirus would work well in the human liver..... In fact, “rodents models might be misleading” for gene therapy, says Jeffrey Bergelson of the Children’s Hospital of Philadelphia” (see pages 954 and 955).

11. Additionally, the Applicants additionally argue in Paper No. 11 that Kang, et al. “report that Fas ligand expression on pancreatic islets results in neutrophilic infiltration and accelerated graft rejection.” The Applicants also state in Paper No. 11 that Chen, et al. report subcutaneous injection of stably transfected colon carcinoma cells that express Fas ligand results in neutrophil activation and rejection of the cancer cells. Hence, expression of Fas ligand does not always inhibit immune responses.” The Applicants also indicate that the regulatory function of Fas ligand is more complex and varies between different experimental and in vivo settings.” Additionally, Chen and Wilson teach that the Applicants’ invention would require the generation of Fas-deficient antigen presenting cells from every patient for the method to work in humans (see page 1012, col. 3). As Applicants stated on page 11 of Paper No. 16, that “It is well known to a person having ordinary skill in this art that one cannot always equate in vitro to in vivo results.” In view of this statement from the Applicants, although a method of inducing systemic immune tolerance in mice using an adenoviral vector is disclosed in the specification, there is no evidence of record to show that one skilled in the art would associate the said *in vivo* mouse method with the successful method of inducing systemic immune tolerance in human, using an adenoviral vector, as claimed herein.
12. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trial and error to practice the claimed invention.

The Applicants argue that their invention encompassed more than the methods of the use of adenoviral vectors in C57BL-6 *lpr/lpr* mice and had demonstrated the use in Fas expressing “normal” mice as well. The Examiner agrees and had withdrawn this grounds for rejection over the claims. However, with the amendment to the claims, all the claims are now drawn to the use of an adenovirus vector encompassing human

therapy. The Applicants have not advanced arguments toward the grounds of rejection over now cancelled claim 19.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

14. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Papers related to this application may be submitted to Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). THE CM1 FAX CENTER TELEPHONE NUMBER IS (703) 305-3014 or (703) 308-4242.

16. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Mary Tung whose telephone number is (703)308-9344. The Examiner can normally be reached Tuesday through Friday from 8:30 am to 6 pm, and on alternating Mondays. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1640 receptionist whose telephone number is (703) 308-0196.

March 23, 2001
Mary B. Tung, Ph.D.
Patent Examiner
Group 1640

David A. Saunders
DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT 182 / 1644